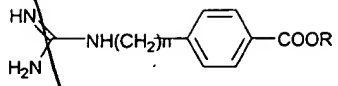
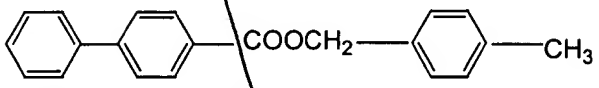
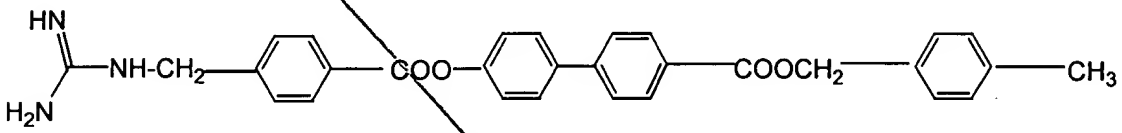


wherein n is 0 or 1, and R is selected from the group consisting of C_{1-10} alkyl, C_{1-10} aryl and



and wherein when n is 0, R is not C_{1-10} aryl.

2. (Amended) The compound of claim 1, which has the following formula II:



or a pharmaceutically acceptable salt thereof.

15. (Amended) The method of claim 5, which further comprises a step of diagnosis or prognosis of *H. pylori* infection in the subject.

REMARKS

Upon entry of the present Amendment, claims 1-20 will be pending. Support for amended claims 1, 2 and 15 can be found throughout the specification and, *inter alia*, in claims 1, 2 and 15 as originally filed. Therefore, the above-described amendments do not introduce any new matter into the present application.

Information disclosure statement

An information disclosure statement, PTO Form 1449, an international search report for the corresponding PCT application (PCT/CN01/01499) and references 1-49 are enclosed herewith. Applicants respectfully request the Examiner to consider and make the references of record in the present application.

Priority

Applicants appreciate the Examiner's acknowledgment of applicants' claim for foreign priority based on an application CN 01142289.0, filed in China on 9/26/2001. A certified copy of the Chinese application will be submitted separately.

Claim objections

Claims 1 and 2 are objected to because of the alleged informalities of not ending with a period as required.

These objections are overcome as amended claims 1 and 2 end with a period.

Rejections under 35 U.S.C. § 112

Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner stated that claim 1 recites the limitation "n is an integer between 0-1." The Examiner also stated that there are no integers between 0 and 1 and the recitation therefore renders claim 1 indefinite.

This rejection is overcome by the amendment of claim 1 wherein "n is an integer between 0-1" is replaced with "n is 0 or 1."

Examiner also stated that the word "pragnosing in line 2 of claim 15 does not appear to be an accepted term of art or word in the standard English vocabulary.

This rejection is overcome by the amendment of claim 15 wherein "diagnosing or pragnosing" is replaced with "diagnosis or prognosis."

It is respectfully submitted that the rejections of claims 1, 2 and 15 under 35 U.S.C. § 112 are overcome by the above amendments and must be withdrawn.

Rejection under 35 U.S.C. § 102

Claim 1 is rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Satoh et al., U.S. Patent No. 4,732,916 (Satoh). Satoh is alleged to disclose the instant claimed carboxylic acid (R = H) of claim 1.

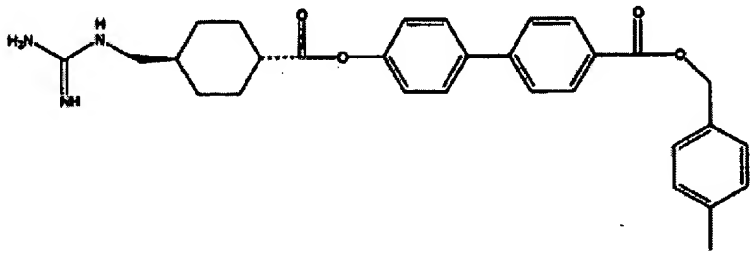
This rejection is overcome by the amendment of claim 1 wherein "R is hydrogen" is no longer recited.

It is respectfully submitted that the rejection of claim 1 under 35 U.S.C. § 102 is overcome by the above amendment and must be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-20 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Kamoda et al., U.S. Patent No. 6,284,791 (Kamoda) in view of Oguro et al., U.S. Patent No. 4,954,512 (Oguro).

Kamoda is alleged to disclose the following compound as a racemic mixture:



The Examiner stated that this corresponds to applicants' claimed compound of instant claim 2 with the exception that the cyclohexane ring is replaced by an aromatic benzene ring. Kamoda is also alleged to disclose the following:

- the activity of the compound against *Helicobacter pylori* and *Escherichia coli*.
- methods of treatment and pharmaceutical compositions (with excipients, etc.) of the compounds disclosed for oral administration to humans.
- combination therapies using the combination of antibiotics such as amoxicillin and omeplazol, lansoplazol (anti-*H. pylori* agents) which comprises inhibition activity to a proton pump and are used in clinics as anti-ulceration agents and compound containing the guanidine group to treat conditions such as gastritis.

The Examiner asserted that the use against resistant strains is implicit in the teaching of combination therapies and the addition written matter does not impart patentability to a kit.

The Examiner acknowledged that Kamoda is silent with regard to replacing the saturated cyclohexane ring with an aromatic benzene ring and the use of an alternative antibacterial agent.

Oguro, however, is alleged to teach genus of closely related anti-ulcer compounds containing the guanidine group. Oguro is further alleged to teach the substitution of an aromatic ring for the saturated cyclohexane ring, and vice-verse in the position in which applicant has modified the structure disclosed by Kamoda by replacing the saturated cyclohexane ring system with an aromatic benzene ring. The Examiner asserted that Oguro's teaching can therefore be seen as a suggestion to modify the compound disclosed by Kamoda to arrive at the instant compound of claim 2. The Examiner concluded that it would have been obvious for one of ordinary skill in the art to have performed the instant invention at the time applicant asserts it was made. The Examiner asserted that the motivation would have been to produce an anti-ulcer treatment that was easier, and thus cheaper, to make since replacement of the trans-cyclohexyl ring with an aromatic ring removes all stereochemistry from the molecule along with the attendant purification issues. The Examiner also asserted that the expectation for success would have been high since both references are directed toward the design of anti-ulcer compounds.

This rejection is respectfully traversed. Kamoda and Oguro, whether alone or in combination, do not render the presently claimed invention obvious for the following reasons.

There is no motivation, whether explicitly or implicitly, to combine the teachings of Kamoda and Oguro to arrive at the presently claimed compounds, pharmaceutical compositions, methods, combinations and kits. The nature of the motivation required in order to justify combining documents in support of an art rejection has been outlined by the Federal Circuit in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998). As there clearly set forth, only three recognized motivations are acceptable. The first is a suggestion in the documents themselves. There is no such suggestion here either in Kamoda or Oguro to combine the teachings of the two references. The second possible rationale lies in the nature of the problem to be solved. What problem would this be? According to the Examiner, the problem to be solved is easier production and lower cost of the compound. However, this alleged problem/solution is nowhere to be found in either Kamoda or Oguro. In fact both patents are concerned with problems not related to production ease or cost. For example, at column 2, lines 58-67, Kamoda states:

> The present inventors took into consideration the above mentioned background and studied compounds with specific and effective antibacterial activity against helicobacter pylori and have achieved the present invention. And the present invention provides compounds comprising superior growth inhibition ability against helicobacter pylori, but do not have the activity against esylhiacori, staphylococcus aureus, methacycline resistant

bacterium, and so on, and a characteristics which is extremely speedy decomposed by actions of decomposition enzyme in intestinum or blood (emphasis added).

At column 2, lines 25-27, Oguro states:

> An object of the present invention is to provide a novel pharmaceutics having a cytoprotection effect providing a more substantial therapy (emphasis added).

From the above stated objectives, it is clear that Kamoda and Oguro address problems related to the drug specificity, metabolism and protectivity, but not production easy or cost. Neither Kamoda nor Oguro teaches or even suggests that replacing the saturated cyclohexane ring with an aromatic benzene ring, as suggested by the Examiner, would make the compounds taught in Kamoda more specific against *Helicobacter pylori* or more quickly decomposed by actions of decomposition enzyme in intestinum or blood. In addition, even assuming *arguendo*, that production easy or cost is a problem to be dealt with Kamoda or Oguro, neither Kamoda nor Oguro teaches or even suggests that replacing the saturated cyclohexane ring with an aromatic benzene ring would make the production of the compounds taught in Kamoda easier or more cost-effective. The third and final criterion is clearly not present - the notorious nature of at least one document cited such that everyone in the field would be expected to be aware of it as the Examiner has not presented any evidence demonstrating that either Kamoda or Oguro is notoriously known in the field.

Another fallacy of the Examiner's reasoning for motivation to combine Kamoda and Oguro to arrive at the presently claimed invention is that it assumes that there is a close structural similarity between compounds taught in Kamoda or Oguro and the presently claimed compound, *i.e.*, compound of claim 2. However, such close structural similarity usually only exists between position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, *e.g.*, by $-CH_2-$ groups). MPEP 2144.09. Isomers having the same empirical formula but different structures are not necessarily considered equivalent by chemists skilled in the art and therefore are not necessarily suggestive of each other. *Ex parte Mowry*, 91 USPQ 219 (Bd. App. 1950) (claimed cyclohexylstyrene not *prima facie* obvious over prior art isohexylstyrene). Similarly, homologs which are far removed from adjacent homologs may not be expected to have similar properties. *In re Mills*, 281 F.2d 218, 126 USPQ 513 (CCPA 1960)

(prior art disclosure of C_8 to C_{12} alkyl sulfates was not sufficient to render *prima facie* obvious claimed C_1 alkyl sulfate).

In the present case, comparing the compounds taught in Kamoda and Oguro and the compound of claim 2, they are neither isomers nor homologs. These compounds have different empirical formulas! It is not proper to compare only the portion of the presently claimed compounds that is different from the prior art compounds to the corresponding portion of the prior art compounds. Rather, the presently claimed compounds must be compared with the prior art compounds as a whole. MPEP 2141.02 *citing Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); and *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious); and *citing W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole."). Compared at the whole compound level, the compounds taught in Kamoda and Oguro and the compound of the present claim 2 have different empirical formulas and are not structurally related at all. In addition, even comparing the saturated cyclohexane ring in the compounds taught in Kamoda with the aromatic benzene ring in the compound of present claim 2, the saturated cyclohexane ring and the aromatic benzene ring have different empirical formulas, have different chemical structures and have different stereochemical structures (*See* WANG Declaration at paragraphs 2-4).

Further, a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. MPEP 2144.09 *citing In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (Affidavit evidence which showed that claimed triethylated compounds possessed anti-inflammatory activity whereas prior art trimethylated compounds did not was sufficient to overcome obviousness rejection based on the homologous relationship between the prior art and claimed compounds.); and *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967) (a 7-fold improvement of activity over the prior art held sufficient to rebut prima facie obviousness based on close structural similarity).

Here, the present inventors have conducted experiments and demonstrated advantages of the compound of present claim 2 (NE-2001) over the compound disclosed in Kamoda (*See* WANG Declaration at paragraph 5). First, the IC_{50} of NE-2001 for inhibiting one of its targets, Proteinase In, is 1.00 μM (See Figure 1 attached herein with WANG Declaration). The IC_{50} of the compound disclosed in Kamoda (shown as TG44 in Figure 1) for inhibiting Proteinase In is 1.54 μM. Therefore, NE-2001 is a more potent inhibitor. In addition, NE-2001's solubility in methanol is almost twice of that of the compound disclosed in Kamoda (shown as TG44 in Table 1 attached herein with WANG Declaration). NE2001 has a solubility of 333 millilitres methanol per gram of NE2001. The compound disclosed in Kamoda (shown as TG44 in Table 1) has a solubility of 540 millilitres methanol per gram of TG44. NE-2001's higher solubility in methanol is beneficial for its formulation and for penetrating the cell wall of *H. pylori* cells. In stark contrast, neither Kamoda nor Oguro teaches or even suggests that replacing the saturated cyclohexane ring with an aromatic benzene ring would make the compound a more potent inhibitor of a protease essential for *Helicobacter pylori* replication or make the compound more beneficial for its formulation and for penetrating the cell wall of *H. pylori* cells.

It is respectfully submitted that the rejection of claims 1-20 under 35 U.S.C. § 103 is overcome by the above remarks and must be withdrawn.

CONCLUSION

Applicants submit that the rejections of claims 1-20 under 35 U.S.C. §§ 102, 103 and 112 have been overcome by the above remarks and/or amendments. Early allowance of the pending claims 1-20 are earnestly requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 524022000100. However,

the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: June 27, 2002 By: _____

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